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(57) Abstract

This invention relates to novel polymer resins, methods for their preparation and their use in the synthesis of compounds or libraries of compounds to be screened as pharmaceutical agents.

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RESINS FOR SOLID STATE SYNTHESIS

FIELD OF THE INVENTION

This invention relates to novel polymer resins, methods for their preparation and their use in the synthesis of libraries of compounds to be screened as pharmaceutical agents.

BACKGROUND OF THE INVENTION

In the continuing search for new chemical moieties that can effectively modulate a variety of biological processes, the standard method for conducting a search is to screen a variety of chemical moieties, for example, naturally occurring compounds, specifically synthesized compounds or compounds which exist in synthetic libraries or data banks. The biological activity of the chemical moieties is determined by employing the moieties in a suitable assay which has been designed to test for a particular property of the chemical moiety being screened, for example, a receptor binding assay which tests the ability of the moiety to bind to a particular receptor site or to exhibit activity at an enzyme.

In an effort to reduce the time and expense involved in screening a large number of randomly chosen compounds for biological activity, several developments have been made in using compounds combined with solid phase synthesis to provide libraries of compounds for the discovery of lead compounds. The chemical generation of molecular diversity has become a major tool in the search for novel lead structures. Currently, the known methods for chemically generating large numbers of molecularly diverse compounds generally involve the use of solid phase synthesis. A wide variety of organic reactions can be carried out on substrates immobilized on resins. As is well known to those of ordinary skill in the art, these include, in addition to peptide synthesis reactions, nucleophilic displacements on benzylic halides, halogenation, nitration, Mitsunobu reaction, sulfonation, oxidation, hydrolysis, acid chloride formation, Friedel-Crafts reactions, reduction with $LiAlH_4$, metallation, and reaction of the organometallic polymer with a wide variety of reagents. See, for example, N. K. Mathur et al., *Polymers as Aids in Organic Chemistry*, Academic Press, New York, p. 18 (1980). In addition, Farrall et al., *J. Org. Chem.*, **41**, p. 3877 (1976) describe the experimental details of some of these reactions carried out with resins.

Methods generally known for generating molecular diversity by utilizing solid phase synthesis typically involve the synthesis and identification of peptides and peptide libraries. See, for example, Lebl et al., *Int. J. Pept. Prot. Res.*, **41**, p. 201 (1993) which discloses methodologies providing selectively cleavable linkers between peptide and resin such that a certain amount of peptide can be liberated from the resin and assayed in soluble form while some of the peptide still remains attached to the resin, where it can be sequenced; Lam et al., *Nature*, **354**, p. 82 (1991) and (WO 92/00091) which disclose a method of synthesis of linear peptides on a solid support such as polystyrene or polyacrylamide resin; Geysen et

al., *J. Immunol. Meth.*, **102**, p. 259 (1987) which discloses the synthesis of peptides on derivatized polystyrene pins which are arranged on a block in such a way that they correspond to the arrangement of wells in a 96-well microtiter plate; and Houghten et al., *Nature*, **354**, p. 84 (1991) and WO 92/09300 which disclose an approach to de novo determination of antibody or receptor binding sequences involving soluble peptide pools.

The major drawback, aside from technical considerations, with all of these methods for lead generation is the quality of the lead. Linear peptides historically have represented relatively poor leads for pharmaceutical design. In particular, there is no rational strategy for conversion of a linear peptide into a non-peptide lead. As noted above, one must resort to screening large databanks of compounds, with each compound being tested individually, in order to determine non-peptide leads for peptide receptors.

It has now been discovered that the instant novel polymer resins are useful in the preparation of either a single compound or a library of molecularly diverse compounds. In particular, the present resins are useful in preparing compounds through resin-bound synthesis, wherein (i) a resin-bound compound intermediate is formed by coupling the instant novel resin with a compound having at least one heteroatom, (ii) the compound portion of the resin-bound compound intermediate is derivatized and (iii) the resin-bound compound intermediate subjected to mild cleavage conditions so that the derivatized compound thus cleaved can have a -COOH, cyclic or acyclic amide, cyclic or acyclic sulfonamide, hydroxy, -NH or -SH group at the position of cleavage from the resin-bound compound intermediate. It will be clear to the skilled artisan that treatment of a compound comprising an -SH group at the cleavage site with, for example, Raney nickel can convert the -SH group to hydrogen. All of the functional groups mentioned above, which remain part of the compound after cleavage from the resin, have unique pharmacological properties, therefore making the compounds comprising them likely candidates as receptor ligands, enzyme inhibitors or channel blockers.

Specifically, after attachment of a compound to the instant novel resins through the novel linker moieties, a large variety of organic reactions can be performed on the compounds (and, in particular, on the functional groups bound to the compounds) without cleavage of the compound from the resin. Therefore, the instant resins and linker moieties allow for efficient preparation and derivatization of compounds to be screened for pharmacological activity. The compounds or libraries of compounds prepared according to this invention may be screened for activity as ligands (either as an agonist or as an

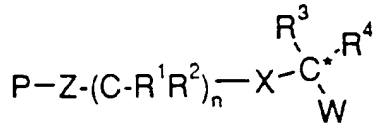
antagonist of the receptor) of various receptor sites, including, but not limited to, G-protein coupled receptor sites, and as enzyme inhibitors, in suitable assays for determining such activity.

The fact that current methods for generation of lead compounds have a variety of limitations, demonstrates the need for new methods for generating and determining compounds as pharmaceutical agents.

The methods disclosed herein may be applied to obtain libraries of compounds that are enzyme inhibitors, receptor ligands or channel blockers.

SUMMARY OF THE INVENTION

This invention relates to novel polymer resins, methods for preparing said resins and intermediates used in the preparation of said resins. The resin comprises the structure of formula (I):



Formula (I)

wherein X is O, S, or N-R, wherein R is hydrogen, alkyl, aryl or arylalkyl; P is a polymer support; Z is a bond, optionally substituted aryl or optionally substituted heteroaryl, wherein the optional substituents are alkyl, aryl, nitro, halogen or methoxy, or Z is -COOR', wherein R' is (C_2 to C_{20}) alkyl optionally having one or more intervening aryl groups; W is a leaving group that is readily displaceable by an oxygen, nitrogen or sulfur anion, including, but not limited to, chlorine, bromine, iodine, $-OSO_2R''$, wherein R" is alkyl, optionally substituted aryl, or perfluoroalkyl; R^1, R^2, R^3 and R^4 are, independently from one another, hydrogen, (C_1 to C_4) alkyl, (C_3 to C_{10}) cyclic alkyl or optionally substituted aryl; and n is an integer from 0 to 10. It will be understood from the description herein that C* is the carbon atom to which the compound to be derivatized is attached after displacement of the leaving group W. This carbon may or may not be a chiral center.

Compounds of formula (I) may be made using syntheses analogous to those described in *Org. Synth.*, Collective Volume 6, p. 101 (1988); *Synthesis*, pp. 762-763 (1983); *Tetrahedron Lett.*, Vol. 28, No. 43, pp. 5125-5128 (1987); *Acta Chimica*

Scandinavica, B 42, pp. 515-523 (1988); *Acta Chimica Scandinavica*, 45, pp. 177-185 (1991); and *J. Med. Chem.*, Vol. 32, pp. 504-516 (1989), all of which are incorporated herein by reference.

One aspect of this invention relates to a novel linker of formula (IA) "-Z-$(CR^1R^2)_n$-X-$(C^*R^3R^4W)$", wherein moieties W, X, Z, R^1, R^2, R^3, R^4, and n are defined as described above.

Therefore, it will be recognized that the novel resin of this invention is the entire compound of formula (I) which comprises the polymer support P, bound to the linker of formula (IA), as defined above.

Another aspect of this invention relates to methods for utilizing solid-phase chemistry to make a compound of formula (II). Using the novel polymer resin of formula (I), a resin-bound compound intermediate is formed by coupling the resin of formula (I) with a compound to be derivatized. Additional synthetic chemistry is performed on the compound portion of the resin-bound compound intermediate, after which a derivatized resin-bound compound intermediate is formed and subjected to cleavage, which cleavage product is the derivatized compound of formula (II). One advantage of the resin of formula (I) is that its structure allows cleavage of the resin-bound compound intermediate, under mild conditions, to result in a compound of formula (II), which compound has a -COOH, cyclic or acyclic amide, cyclic or acyclic sulfonamide, hydroxy, -NH or -SH group on the compound at the position of cleavage from the resin-bound compound intermediate.

The compound of formula (II) comprises the following structure:

A-H

Formula (II)

wherein A is A_1, A_2, A_3, A_4, A_5, A_6, A_7, or A_8;

A_1 is $-OR^5$, wherein R^5 is optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbonyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted heteroarylalkyl, optionally substituted heterocyclic, optionally substituted heteroalkyl, optionally substituted heterocyclicalkyl, or optionally substituted alkylheteroalkyl;

A_2 is $-NR^6R^7$, wherein R^6 and R^7 are the same or different and are hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted heteroarylalkyl, optionally substituted heterocyclic, optionally substituted heteroalkyl, optionally substituted heterocyclicalkyl, or optionally substituted alkylheteroalkyl, provided that R^6 and R^7 cannot both be hydrogen; or wherein R^6 and R^7, together with the nitrogen to which they are bound, form an optionally substituted, saturated or unsaturated, 4-, 5-, 6- or 7-membered ring;

A_3 is $-SR^8$, wherein R^8 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted cycloalkyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted heteroarylalkyl, optionally substituted heterocyclic, optionally substituted heteroalkyl, optionally substituted heterocyclicalkyl, or optionally substituted alkylheteroalkyl;

A_4 is R^9-COO^-, wherein R^9 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted cycloalkyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted heteroarylalkyl, optionally substituted heterocyclic, optionally substituted heteroalkyl, optionally substituted heterocyclicalkyl, or optionally substituted alkylheteroalkyl;

A_5 is $-NR^{10}$-$C(O)R^{11}$, wherein R^{10} and R^{11} are the same or different and are optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted heteroarylalkyl, optionally substituted heterocyclic, optionally substituted heteroalkyl, optionally substituted heterocyclicalkyl, or optionally substituted alkylheteroalkyl, or wherein R^{10} and R^{11}, together with the nitrogen and carbonyl to which they are bound, form an optionally substituted, saturated or unsaturated, 4-, 5-, 6- or 7-membered ring;

A_6 is $-NR^{12}$-SO_2R^{13}, wherein R^{12} and R^{13} are the same or different and are optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted heteroarylalkyl, optionally substituted heterocyclic, optionally substituted heteroalkyl, optionally substituted heterocyclicalkyl, or optionally substituted alkylheteroalkyl; or wherein R^{12} and R^{13}, together with the nitrogen

and sulfone to which they are bound, form an optionally substituted, saturated or unsaturated, 4-, 5-, 6- or 7-membered ring;

A_7 is $-O-(CH_2)_m-C(O)R^{14}$, wherein m is an integer from 0 to 10; and R^{14} is hydrogen, hydroxyl, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted heteroarylalkyl, optionally substituted heterocyclic, optionally substituted heteroalkyl, optionally substituted heterocyclicalkyl, or optionally substituted alkylheteroalkyl; or wherein when m is an integer from 1 to 10, R^{14} may form an optionally substituted, saturated or unsaturated, 4-, 5-, 6- or 7-membered ring together with one of the methylene carbons; and

A_8 is $-O-(CH_2)_r-A'-C(O)R^{15}$, wherein r is an integer from 0 to 10; A' is O, N, or S; and R^{15} is hydrogen, hydroxyl, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted heteroarylalkyl, optionally substituted heterocyclic, optionally substituted heteroalkyl, optionally substituted heterocyclicalkyl, or optionally substituted alkylheteroalkyl, optionally substituted heterocyclicalkyl, or optionally substituted alkylheteroalkyl; or R^{15} may form an optionally substituted, saturated or unsaturated, 4-, 5-, 6- or 7-membered ring together with one of the methylene carbons; provided that when A' is O or S, r must be an integer from 1 to 10.

Yet another aspect of this invention relates to methods for preparing resin-bound compounds of formula (II). Still another aspect is this invention relates to methods for utilizing novel polymer resin intermediates for preparing the compounds of this invention. Yet further, this invention relates to methods for preparing a library of molecularly diverse compounds of formula (II), wherein said methods utilize the polymer resins of this invention in combinatorial synthesis methods. Still further, this invention relates to methods for screening the compounds synthesized by the methods of this invention as pharmaceutical agents.

DETAILED DESCRIPTION OF THE INVENTION

The terms "resin-bound synthesis" and "solid phase synthesis" are used herein interchangeably to mean one or a series of chemical reactions used to prepare either a

single compound of formula (II) or a library of molecularly diverse compounds of formula (II), wherein the chemical reactions are performed on a compound to be derivatized, which compound is bound to a polymer support through a novel linkage, in particular, a linkage moiety comprised of any combination of any two of N, O or S heteroatoms which are separated by a carbon atom, wherein any one of the N, O or S heteroatoms is part of the compound to be derivatized. In a preferred embodiment of this invention, the heteroatoms are separated by a methylene group.

The terms "compound intermediate" or "resin-bound compound intermediate" are used herein at all occurrences to mean an intermediate formed by the displacement of leaving group W of formula (I) with a compound to be derivatized comprising at least one heteroatom, which heteroatom is bound directly to a carbon atom (C*) to form a carbon atom-heteroatom bond, wherein this carbon is directly bound to a second heteroatom (variable X), which second heteroatom joins the carbon atom (C*), through a moiety $-Z-(CR^1R^2)_n-$, to a polymer backbone, P. It will be recognized by the skilled artisan that the leaving group W is being displaced by an oxygen, nitrogen or sulfur heteroatom of the compound to be derivatized thus forming the carbon atom-heteroatom bond/linkage.

It will be recognized that the carbon atom C*, is depicted as such in order to indicate the position of attachment of the compound to be derivatized to the resin, thus forming the resin-bound compound intermediate. The carbon atom C* may or may not be a chiral center.

The terms "polymeric resin," "polymer support" or "polymer backbone" are used herein at all occurrences to mean any of a number of aliphatic or aromatic polymers, copolymers or combinations of polymers which lack functionality known to participate in the additional synthetic chemistry performed for generation of the instant derivatized compound(s) of formula (II). In particular, the terms may include a bead or other solid support such as pellets, disks, capillaries, hollow fibers, needles, solid fibers, pins, cellulose beads, pore-glass beads, silica gels, or latex beads, made of, for example, a crosslinked polystyrene resin, a polyethylene glycol-polystyrene based resin, a polypropylene glycol based resin, polyamide, polysulfamide, phenolic resins, polysaccharides and any other substance which may be used as such and which would be known or obvious to one of ordinary skill in the art. Preferred polymeric resins for use herein are cross-linked polystyrene based resins, polyethylene glycol-polystyrene based resins and polypropylene glycol based resins. After the desired compound (or library of compounds) is synthesized

as part of a resin-bound compound intermediate, it may then be cleaved from the resin-bound compound intermediate (hereinafter referred to as a "soluble compound" or a "soluble library"). The compounds made by the instant methods may also remain bound as a resin-bound compound intermediate which is used to perform the resin-bound synthesis (hereinafter referred to as "resin-bound compounds" or "resin-bound libraries").

The term "additional synthetic chemistry" is used herein at all occurrences to mean chemical reactions which are performed on the resin-bound compound intermediate in order to derivatize the compound portion of the intermediate. The additional synthetic chemistry is performed after attachment of the compound to be derivatized to the resin of formula (I), and prior to cleavage of the derivatized compound from the polymeric resin. It will be understood that said chemical reactions are compatible with and non-reactive with the resin-bound compound intermediate and may be used to derivatize the compound bound to the resin in order to produce compounds of formula (II) which are the final products after cleavage of the resin-bound compound intermediate. Methods similar to those known in the art regarding acetals, hemithioacetals, dithioacetals and aminoacetals may be used for preparing resin-bound compound intermediates from a resin of formula (I) and for cleaving the resin-bound compound intermediates in order to produce compounds of formula (II). Suitable methods of cleaving the resin-bound organic compounds disclosed herein from the linkage to the resin may be found in Protective Groups in Organic Synthesis, 2nd Edition, T. Greene and P.G.M. Wuts, pp. 17-24; 47-55; 149-150; 156-158; 279-282; 393-394; 413-416; 437-440; and 449-452 (1991). It will be understood by the skilled artisan that the additional synthetic chemistry performed on the compound intermediate, is done so prior to cleavage of the carbon atom-heteroatom bond that links the resin of formula (I) to the compound to be derivatized. Certain chemical reaction conditions are incompatible with the carbon atom-heteroatom linkage, i.e., they cause cleavage of the carbon atom-heteroatom linkage prior to completing the steps needed to derivatize the compound attached to the resin. Therefore, those chemical reactions are not among the additional synthetic chemistry that may be used in the methods of this invention. For example, reactions which require strong acid are incompatible with the carbon-oxygen and carbon-nitrogen containing linkages; and reactions which require strong oxidants are incompatible with the carbon-sulfur containing linkages.

The term "assay" is used herein at all occurrences to mean a binding assay or a functional assay known or obvious to one of ordinary skill in the art, including, but not

limited to, the assays disclosed herein. A particularly suitable assay for use according to this invention is disclosed by Lerner et al., *Proc. Natl. Acad. Sci. U.S.A.*, **91**(5), pp. 1614-1618 (1994).

The term "alkyl" is used herein at all occurrences to mean a straight or branched chain radical of 1 to 20 carbon atoms, unless the length is limited thereto, including, but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, and the like. Preferably, the alkyl chain is 1 to 10 carbon atoms in length; more preferably, 1 to 8 carbon atoms in length.

The terms "cycloalkyl" and "cyclic alkyl" are used herein at all occurrences to mean cyclic radicals, preferably comprising 3 to 10 carbon atoms which may be mono- or bicyclo- fused ring systems which may additionally include unsaturation, including, but not limited to, cyclopropyl, cyclopentyl, cyclohexyl, 1,2,3,4-tetrahydronaphthyl, and the like.

The term "alkenyl" is used herein at all occurrences to mean a straight or branched chain radical of 2 to 20 carbon atoms, unless the length is limited thereto, wherein there is at least one double bond between two of the carbon atoms in the chain, including, but not limited to, ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, and the like. Preferably, the alkenyl chain is 2 to 10 carbon atoms in length; more preferably, 2 to 8 carbon atoms in length.

The term "alkynyl" is used herein at all occurrences to mean a straight or branched chain radical of 2 to 20 carbon atoms, unless the chain length is limited thereto, wherein there is at least one triple bond between two of the carbon atoms in the chain, including, but not limited to, acetylene, 1- propylene, 2-propylene, and the like. Preferably, the alkynyl chain is 2 to 10 carbon atoms in length; more preferably, 2 to 8 carbon atoms in length.

In all instances herein where there is an alkenyl or alkynyl moiety as a substituent group (whether optionally substituted or not), such as defined for A_1, A_2, A_3, A_4, A_5, A_6, A_7, or A_8 above, the unsaturated linkage, i.e., the vinylene or acetylene linkage is preferably not directly attached to the nitrogen, oxygen or sulfur moieties.

The term "alkoxy" is used herein at all occurrences to mean a straight or branched chain radical of 1 to 20 carbon atoms, unless the chain length is limited thereto, bonded to an oxygen atom, including, but not limited to, methoxy, ethoxy, n- propoxy, isopropoxy, and the like. Preferably, the alkyl chain of the alkoxy moiety is 1 to 10 carbon atoms in length; more preferably 1 to 8 carbon atoms in length.

The term "aryl" is used herein at all occurrences to mean 5-14-membered substituted or unsubstituted aromatic ring(s) or ring systems which may include bi- or tri-cyclic systems, including, but not limited to phenyl, naphthyl, and the like.

The term "heteroatom" is used herein at all occurrences to mean an oxygen atom, a sulfur atom or a nitrogen atom. It will be recognized that when the heteroatom is nitrogen, it may form an NR_aR_b moiety, wherein R_a and R_b are, independently, hydrogen or C_1 to C_8 alkyl, or together with the nitrogen to which they are bound, form a saturated or unsaturated 5-, 6- or 7-membered ring, including, but not limited to, pyrrolidine, piperidine, piperazine, morpholine, pyridine, and the like. It will be recognized that the saturated or unsaturated 5-, 6- or 7-membered ring may optionally have one or more additional heteroatoms in the ring.

The term "heteroaryl" is used herein at all occurrences to mean 5-14-membered substituted or unsubstituted aromatic ring(s) or ring systems which may include bi- or tri-cyclic systems in which one or more of the rings comprise one or more heteroatoms. Representative examples include, but are not limited to, pyrrole, thiophene, pyridine, pyrimidine, oxazole, quinoline, thiazole, isoquinoline, imidazole, benzimidazole, furanyl, and the like.

The term "heterocyclic" is used herein at all occurrences to mean a saturated or wholly or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more heteroatoms, including, but not limited to, pyrrolidine, piperidine, piperazine, morpholine, imidazolidine, pyrazolidine, benzodiazepines, and the like.

The terms "arylalkyl", "heteroarylalkyl" and "heterocyclicalkyl" are used herein at all occurrences to mean an aryl, heteroaryl or heterocyclic moiety as defined above, which are connected to a C_1 to C_{20} (preferably C_1 to C_{10}; more preferably C_1 to C_8) alkyl moiety as defined above, for example, benzyl or phenethyl, and the like.

The term "heteroalkyl" is used herein at all occurrences to mean a straight or branched chain radical of 1 to 20 carbon atoms (preferably C_1 to C_{10}; more preferably C_1 to C_8), unless the chain is limited thereto, wherein the chain comprises one or more heteroatoms. Representative examples include, but are not limited to, A_1 is OR^5, wherein R^5 is heteroalkyl, and may be represented by the formula $-CH_2-S-CH_2-NH_2$. It will be recognized by one of skill in the art that when the heteroatom of the heteroalkyl moiety is oxygen or sulfur, it is not directly attached to the oxygen atom of A_1, A_7 or A_8; or when

the heteroatom of the heteroalkyl moiety is oxygen, it is not directly attached to the sulfur atom of A_3.

The term "alkylheteroalkyl" is used herein at all occurrences to mean a straight or branched chain radical of 1 to 20 carbon atoms (preferably C_1 to C_{10}; more preferably C_1 to C_8), unless the length is limited thereto, wherein the chain comprises one or more heteroatoms. Representative examples include, but are not limited to, methylethyl ether, ethyl propyl sulfide, isopropylthiobutane, dimethyl amine, diethylmethylamine, dimethyl sulfone, dimethyl sulfoxide, and the like.

The term "halogen" is used herein at all occurrences to mean chloro, fluoro, iodo and bromo.

The term "cyclic amide" is used herein at all occurrences to mean that the nitrogen and the carbonyl of an amide moiety, together with the R groups to which they are attached, form a saturated or unsaturated 4-, 5-, 6- or 7-membered ring. It will be recognized that the saturated or unsaturated 4-, 5-, 6- or 7-membered ring may optionally have one or more additional heteroatoms in the ring.

The term "cyclic sulfonamide" is used herein at all occurrences to mean that the nitrogen and the sulfone of a sulfonamide, together with the R groups to which they are attached, form a saturated or unsaturated 4-, 5-, 6- or 7-membered ring. It will be recognized that the saturated or unsaturated 4-, 5-, 6- or 7-membered ring may optionally have one or more additional heteroatoms in the ring.

The term "optionally substituted", unless defined otherwise, is used herein at all occurrences to mean that the moieties may or may not be substituted with one to five various functional groups including, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, arylalkyl, heteroarylalkyl, halogen, NO_2, -OR'", -SR'", $-N(R'")_2$, -NHC(O)R'", $SO_2N(R'")_2$, $-CO_2R'"$ or $-CON(R'")_2$, wherein R'" is hydrogen, (C_1 - C_6) alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclic, heterocyclicalkyl, including, but not limited to, phenyl, benzyl, pyridyl, and the like. In the case of the optional substituent being $-N(R'")_2$, $SO_2N(R'")_2$ or $-CON(R'")_2$, it will be clear to the skilled artisan that the R'" groups attached to the nitrogen may be the same or different.

For purposes herein, when the optional substituent attached to any of R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14} or R^{15}, is alkyl, aryl, cycloalkyl, arylalkyl, alkylheteroalkyl, heteroarylalkyl, -OR'", -SR'", $-N(R'")_2$, -NHC(O)R'", $SO_2N(R'")_2$, $-CO_2R'"$ or $-CON(R'")_2$, it will be recognized that the alkyl, aryl, cycloalkyl, arylalkyl, alkylheteroalkyl,

heteroarylalkyl moiety or the moiety R''' may be optionally substituted with one to five various optionally substituted functional groups including alkyl, alkenyl, aryl, cycloalkyl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclic or heterocyclicalkyl.

The terms "combinatorial library" or "library of molecularly diverse compounds" are used herein at all occurrences to mean a collection of diverse compounds of formula (II) which have been synthesized simultaneously starting from a core compound structure. The library contains a discrete number of independently variable substituents, functional groups or structural elements. Further, the library is designed so that, for the range of chemical moieties selected for each of the independently variable substituents, compounds containing all possible permutations of those substituents may be present in the library. Thus, by way of illustration, if a compound to be derivatized into a compound of formula (II) contains three independently variable substituents, labeled X, Y and Z, and if X is taken from *m* different chemical moieties, Y from *n* different chemical moieties and Z from *p* different chemical moieties (wherein *m*, *n* and *p* are integers which define the size of the library, and which range between 1 and 100,000; between 1 and 10,000; between 1 and 1,000; between 1 and 100; and between 1 and 50), then the library may contain *m* x *n* x *p* different chemical compounds and all possible combinations of X, Y and Z could be present on the compounds within that library. The methods for preparing combinatorial libraries of compounds are such that the molecularly diverse compound members of the libraries are synthesized simultaneously.

The term "G-protein coupled receptor(s)" is used herein at all occurrences to mean a membrane receptor using G-proteins as part of their signaling mechanism, including, but not limited to muscarinic acetylcholine receptors, adenosine receptors, adrenergic receptors, IL-8R receptors, dopamine receptors, endothelin receptors, histamine receptors, calcitonin receptors, angiotensin receptors and the like.

It has now been discovered that optionally substituted compounds of formula (II) can be prepared by resin-bound synthesis, wherein said compound, after cleavage from a novel polymeric resin-bound compound intermediate, has a -COOH, cyclic or acyclic amide, cyclic or acyclic sulfonamide, hydroxy, -NH or -SH group on the carbon where it was bound to the resin. The compound of formula (II) is as follows:

A-H

Formula (II)

wherein A is A_1, A_2, A_3, A_4, A_5, A_6, A_7, or A_8; and

A_1 is $-OR^5$, wherein R^5 is optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbonyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted heteroarylalkyl, optionally substituted heterocyclic, optionally substituted heteroalkyl, optionally substituted heterocyclicalkyl, or optionally substituted alkylheteroalkyl. A preferred embodiment of this invention comprises a compound of formula (II), wherein A is A_1, i.e., $-OR^5$, wherein R^5 is optionally substituted aryl, and one of the optional substituents is $CON(R''')_2$ wherein at least one of the R''' moieties attached to the amide nitrogen is optionally substituted heterocyclicalkyl, including, but not limited to, N-ethyl pyrrolidine. Another preferred embodiment of this invention comprises a compound of formula (II), wherein A is A_1, i.e., $-OR^5$, wherein R^5 is optionally substituted cycloalkyl, preferably optionally substituted 1,2,3,4-tetrahydronaphthyl, wherein one the optional substituents on the cycloalkyl ring is $-N(R''')_2$ and wherein R''', independently, is C_1 to C_6 alkyl and optionally substituted C_1 to C_6 alkyl, wherein the optional substituent on the alkyl moiety is aryl, preferably phenyl.

A_2 is $-NR^6R^7$, wherein R^6 and R^7 are the same or different and are hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted heteroarylalkyl, optionally substituted heterocyclic, optionally substituted heteroalkyl, optionally substituted heterocyclicalkyl, or optionally substituted alkylheteroalkyl, provided that R^6 and R^7 cannot both be hydrogen; or wherein R^6 and R^7, together with the nitrogen to which they are bound, form an optionally substituted, saturated or unsaturated, 4-, 5-, 6- or 7-membered ring.

A_3 is $-SR^8$, wherein R^8 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted cycloalkyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted heteroarylalkyl, optionally substituted heterocyclic, optionally substituted heteroalkyl, optionally substituted heterocyclicalkyl, or optionally substituted alkylheteroalkyl.

A_4 is R^9-COO^-, wherein R^9 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted cycloalkyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted heteroarylalkyl, optionally substituted heterocyclic, optionally

substituted heteroalkyl, optionally substituted heterocyclicalkyl, or optionally substituted alkylheteroalkyl. From the description herein, it will be understood that when A is A_4, i.e., R^9-COO^-, the carboxy oxygen is directly linked to the novel resin of formula (I) through a carbon atom-heteroatom bond and that the linkage is not directly through R^9. A preferred embodiment of this invention comprises a compound of formula (II) wherein A is A_4, i.e., R^9-COO^-, wherein R^9 is optionally substituted aryl, and one of the optional substituents is heteroarylalkyl which is further substituted by a (C_1 to C_6) alkyl and an optionally substituted (C_2 to C_6) alkenyl moiety, wherein the optional substituents on the alkenyl moiety are $-CO_2R'''$, wherein R''' is (C_1 to C_6) alkyl; and a heteroaryl moiety, for example, thiophene.

A_5 is $-NR^{10}-C(O)R^{11}$, wherein R^{10} and R^{11} are the same or different and are optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted heteroarylalkyl, optionally substituted heterocyclic, optionally substituted heteroalkyl, optionally substituted heterocyclicalkyl, or optionally substituted alkylheteroalkyl; or wherein R^{10} and R^{11}, together with the nitrogen and carbonyl to which they are bound, form an optionally substituted, saturated or unsaturated, 4-, 5-, 6- or 7-membered ring.

A_6 is $-NR^{12}-SO_2R^{13}$, wherein R^{12} and R^{13} are the same or different and are optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted heteroarylaikyl, optionally substituted heterocyclic, optionally substituted heteroalkyl, optionally substituted heterocyclicalkyl, or optionally substituted alkylheteroalkyl; or wherein R^{12} and R^{13}, together with the nitrogen and sulfone to which they are bound, form an optionally substituted, saturated or unsaturated, 4-, 5-, 6- or 7-membered ring.

A_7 is $-O-(CH_2)_m-C(O)R^{14}$, wherein m is an integer from 0 to 10; and R^{14} is hydrogen, hydroxyl, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted heteroarylalkyl, optionally substituted heterocyclic, optionally substituted heteroalkyl, optionally substituted heterocyclicalkyl, or optionally substituted alkylheteroalkyl; or wherein when m is an integer from 1 to 10, R^{14} may form an optionally substituted,

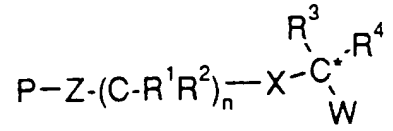
saturated or unsaturated, 4-, 5-, 6- or 7-membered ring together with one of the methylene carbons.

A_8 is -O-$(CH_2)_r$-A'-C(O)R^{15}, wherein r is an integer from 0 to 10; A' is O, N, or S; and R^{15} is hydrogen, hydroxyl, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted heteroarylalkyl, optionally substituted heterocyclic, optionally substituted heteroalkyl, optionally substituted heterocyclicalkyl, or optionally substituted alkylheteroalkyl; or R^{15} may form an optionally substituted, saturated or unsaturated, 4-, 5-, 6- or 7-membered ring together with one of the methylene carbons; provided that when A' is O or S, r must be an integer from 1 to 10.

In contrast to the resins known in the art, the instant polymer resins and linkage moieties are particularly useful in preparing compounds of formula (II) by resin-bound synthesis. The instant resin may be coupled with a compound (or a plurality of compounds) in order to form a resin-bound compound intermediate (or a plurality of resin-bound compound intermediates). Because of the structure of the resin of formula (I), cleavage of the carbon atom-heteroatom bond of the resin-bound compound intermediate to yield a compound of formula (II) which has a -COOH, cyclic or acyclic amide, cyclic or acyclic sulfonamide, hydroxy, -NH or -SH group at the cleavage position, is synthetically possible. Each of these groups offers its own unique pharmacological properties. Further, the instant resins and linkage moieties allow a variety of chemical reactions, or additional synthetic chemistry, to be conducted on compounds attached thereto, without cleavage of the compound from the resin until the attached compounds are fully derivatized. After derivatization, the attached compounds may be cleaved from the resin by cleaving the carbon atom-heteroatom bond of the resin-bound compound intermediate, for example, using mild acid conditions, in order to produce compounds of formula (II). In addition, the polymer resins of this invention also allow the successful preparation of libraries of molecularly diverse compounds which, upon cleavage from the resin, have a -COOH, cyclic or acyclic amide, cyclic or acyclic sulfonamide, hydroxy, -NH or -SH group at the cleavage position. The compounds prepared by the methods described herein can be screened in assays developed for determining lead compounds as pharmaceutical agents.

In one aspect, the invention is in a method for preparing a compound of formula (II) by resin-bound synthesis, said method comprising the steps of:

(i) attaching a compound comprising at least one heteroatom to a polymeric resin of formula (I):



Formula (I)

wherein X is O, S, or N-R, wherein R is hydrogen, alkyl, aryl or arylalkyl; P is a polymer support; Z is a bond, optionally substituted aryl or optionally substituted heteroaryl, wherein the optional substituents are alkyl, aryl, nitro, halogen or methoxy, or Z is -COOR', wherein R' is (C_2 to C_{20}) alkyl optionally having one or more intervening aryl groups; W is a leaving group that is readily displaceable by an oxygen, nitrogen or sulfur anion, including, but not limited to, chlorine, bromine, iodine, $-OSO_2R''$, wherein R" is alkyl, optionally substituted aryl, or perfluoroalkyl; R^1, R^2, R^3 and R^4 are, independently from one another, hydrogen, (C_1 to C_4) alkyl, (C_3 to C_{10}) cyclic alkyl or optionally substituted aryl; and n is an integer from 0 to 10, whereby the attachment occurs by displacing the leaving group W with a heteroatom of the compound being attached to the resin, to form a resin-bound compound intermediate having a carbon atom-heteroatom bond at the carbon atom indicated with an asterisk;

(ii) performing additional synthetic chemistry on the compound attached to the resin-bound compound intermediate; and

(iii) cleaving the carbon atom-heteroatom bond of the resin-bound compound intermediate so that the compound thus formed has a -COOH, cyclic or acyclic amide, cyclic or acyclic sulfonamide, hydroxy, -NH or -SH group on the carbon where it was bound to a polymeric resin, prior to cleavage therefrom.

It will be clear to one of ordinary skill in the art that one suitable method according to this invention for attaching the compound to be derivatized to a resin of formula (I), is by an S_N2 displacement of moiety W with the heteroatom used to link the compound to the resin. For example, as depicted in Scheme 1 below, 3-Scheme 1 is attached to the resin of formula (I) wherein P is a polystyrene backbone; Z is phenyl; X is O; W is chlorine; and R^1, R^2, R^3 and R^4 are each hydrogen, i.e., 2-Scheme 1, by forming an anion of the oxygen heteroatom of 3-Scheme 1 using a strong base (such as NaH or Cs_2CO_3) in an aprotic

solvent (such as THF, CH_2Cl_2, dioxane or Dimethylformamide ("DMF")), which anion displaces the chlorine atom (W) of resin 2-Scheme 1, thereby producing the resin-bound compound intermediate 4-Scheme 1. According to this invention, additional synthetic chemistry may be performed on the compound intermediate in order to further derivatize the compound. As described above, the additional synthetic chemistry performed in order to modify the compound must be such that the compound is derivatized without cleaving the carbon-heteroatom bond of the resin-bound compound intermediate.

According to this invention, the compound to be derivatized in order to produce a compound of formula (II), is bound to a polymer resin through a carbon-heteroatom bond to give a resin-bound compound intermediate. It will be understood that the compound to be derivatized will comprise at least one heteroatom which is to be linked to the polymer support through a carbon atom of a linker group (i.e., C*). In particular, the compound is bound to the polymer support through a linker group of formula (IA) comprising the following moiety - "-Z-$(CR^1R^2)_n$-X-$(C^*R^3R^4W)$", wherein Z is defined as an optionally substituted aryl group or an optionally substituted heteroaryl group, wherein the optional substituents are alkyl, aryl, nitro, halogen or methoxy, or Z is -COOR', wherein R' is (C_2 to C_{20}) alkyl optionally having one or more intervening aryl groups; X is a heteroatom; W is a leaving group that is readily displaceable by an oxygen, nitrogen or sulfur anion, including, but not limited to, chlorine, bromine, iodine, $-OSO_2R$", wherein R" is alkyl, optionally substituted aryl, or perfluoroalkyl; R^1, R^2, R^3 and R^4 are, independently from one another, hydrogen, (C_1 to C_4) alkyl, (C_3 to C_{10}) cyclic alkyl or optionally substituted aryl; C* is the carbon atom through which the compound to be derivatized is bound to the polymer support; and n is an integer from 0 to 10. Z is preferably an optionally substituted aryl moiety, more preferably, an optionally substituted phenyl moiety. Preferred optional substituents on moiety Z are nitro, halogen and/or methoxy. Of course, it will be obvious to one of ordinary skill in the art that in order for the compound to be linked to the resin, the heteroatom of the compound must displace moiety W of the linker, so that a resin-bound compound intermediate is produced. It will be recognized by the skilled artisan that conventional procedures may be used in order to attach the linker to the polymer support P, so that a compound of formula (I) is produced. For example, the linker may be reacted with a chloromethyl cross-linked divinylbenzene polystyrene resin.

Preferred linker groups of formula (IA), i.e., Z-$(C\text{-}R^1R^2)_n$-X-$(C^*\text{-}R^3R^4W)$, for use in the methods disclosed herein include, but are not limited to, the following linker groups:

-Ph-CH_2-O-CH_2Cl-, wherein Z is phenyl ("Ph"); X is O; and R^1, R^2, R^3 and R^4 are each hydrogen; W is Cl and n is 1; or -Ph-CH_2-S-CH_2Cl-, wherein Z is phenyl; X is S; and R^1, R^2, R^3 and R^4 are each hydrogen; W is Cl and n is 1. It will be understood that when Z is optionally substituted phenyl, and the polymer support is polystyrene-based, e.g., a chloromethylpolystyrene resin known as the Merrifield resin, the optionally substituted phenyl moiety that is Z, is also part of the polymer resin. The polymer support is then further functionalized in order to couple the remaining portion of the linker to the polymer support using methods such as those shown in Schemes 1 and 2, below.

In order to cleave the carbon atom-heteroatom linkage of the resin-bound compound intermediate while leaving a -COOH, cyclic or acyclic amide, cyclic or acyclic sulfonamide, hydroxy, -NH or -SH group at the cleavage site, one may use a number of suitable conditions. Specifically, conditions conventionally known to be capable of cleaving acetals, hemithioacetals and dithioacetals may be used. For example, cleavage may be accomplished by treating the resin-bound compound intermediate with a strong protic acid. In particular, the acidic cleavage conditions, include, but are not limited to, treatment with trifluoroacetic acid ("TFA"), hydrofluoric acid ("HF"), hydrochloric acid ("HCl"), hydrobromic acid ("HBr"), pyridinium hydrofluoride, sulfuric acid ("H_2SO_4"), trifluormethanesulfonic acid (commonly referred to as triflic acid), boron trifluoride ("BF_3"), methanesulfonic acid or mixtures thereof. Cleavage methods may be carried out in solution or by applying the acid to the resin-bound compound intermediate(s), neat. Preferred cleavage conditions utilize 25% TFA. Further, an addition of 1% veratrol or ethanedithiol to the cleavage mixture may be used to prevent undesirable side reactions of the liberated compound of formula (II).

Alternatively, cleavage of the carbon-heteroatom bond for linker groups with sulfur heteroatoms, may be accomplished with silver or mercury salts using conditions known to one of ordinary skill in the art. It will also be clear to the skilled artisan that when the methods disclosed herein are used to make a compound or a library of compounds of formula (II), wherein A is A_3, i.e.,-SR^8, after additional synthetic chemistry is performed and the compound(s) has been cleaved from the resin, the end-product compound of formula (II) may be desulfurized using conditions known in the art, such as treatment with Raney nickel, in order to produce a compound which contains a hydrogen at the position where the compound was attached to the resin.

In another aspect, the invention is in a method for preparing a compound of formula (II) which is resin-bound, said process comprising the steps of:

(i) attaching a compound comprising at least one heteroatom to a polymeric resin of formula (I) as defined above, whereby the attachment occurs by displacing the leaving group W to form a resin-bound compound intermediate having a carbon atom-heteroatom bond at the carbon indicated with an asterisk; and

(ii) optionally performing additional synthetic chemistry on the compound attached to the resin.

In this aspect of the invention, the resin-bound compound intermediate may be derivatized immediately by modifying the compound with additional synthetic chemistry or stored for future derivatization of the resin-bound compound. If the compound intermediate is derivatized, the resulting derivatized resin-bound compound intermediate is a precursor to the compound of formula (II), wherein after cleavage, the compound is a compound of formula (II), i.e., it has a -COOH, cyclic or acyclic amide, cyclic or acyclic sulfonamide, hydroxy, -NH or -SH group on the carbon where it was bound to a polymeric resin. The resin-bound compounds prepared according to this invention may be screened as pharmaceutical agents in the assays described below.

In yet another aspect, this invention is in a method for preparing a library of molecularly diverse compounds, each comprising at least one heteroatom, by resin-bound synthesis, said method comprising the steps of:

(i) attaching a heteroatom of each of a plurality of compounds to an individual polymeric resin of formula (I) by displacing each of the leaving groups W on the individual polymeric resins to give a plurality of resin-bound compound intermediates;

(ii) optionally dividing said resin-bound compound intermediates into a plurality of portions;

(iii) performing additional synthetic chemistry on the plurality of resin-bound compound intermediates to derivatize said compounds; and

(iv) optionally recombining the portions.

Based upon the disclosure herein, it will be clear to one of ordinary skill in the art that there are many possible synthetic approaches to creating the libraries of this invention. The libraries are considered to be combinatorial libraries because the compounds generated from the synthetic methods are molecularly diverse and are prepared simultaneously. The libraries are prepared on the polymer resins using the linkers described herein. For

example, a plurality of compounds comprising at least one heteroatom, are each attached to an individual polymer resin support of formula (I) through a carbon-heteroatom bond to give a plurality of resin-bound compound intermediates. In a first step modification of the compound attached to the resin, the plurality of resin-bound compound intermediates may be reacted with one or more reagents, in one reaction vessel. Alternatively, in a first step modification, aliquots of the resin-bound compound intermediates may be reacted with one or more reagents; each one of which will modify the compound attached to the resin as a resin-bound compound intermediate; and then the resultant product in each separate aliquot is mixed together with the products formed in the other aliquots to form the library of derivatized compounds. This first modified/derivatized library may then be further derivatized by repeating the process of dividing and recombining the derivatized resin-bound compound intermediates formed by the additional synthetic chemistry. Suitably, when the libraries of the invention are prepared according to the instant disclosure, each polymer support unit, for example, a bead, bears a single derivatized compound species created by the additional synthetic chemistry performed on the resin-bound compound intermediate.

It will be obvious to one of skill in the art that the steps of optionally dividing and recombining the resin-bound compound intermediates into portions are for purposes of varying the derivatization on the compounds which are generated by the combinatorial synthesis. See, for example, Moss et al., *Ann. Rep. Med. Chem.*, **28**, p. 315 (1993) for the split-synthesis method of preparing peptide libraries of compounds, variations on which may be used to prepare the non-peptide libraries of this invention. It will also be obvious to the skilled artisan that the resin-bound compound intermediates may be divided into portions at any point during the synthetic scheme. The portions may be recombined at any point during the scheme or, further iterations may be applied if more derivatization is required. For example, after a first step modification where the aliquots were divided and reacted with one or more appropriate reagents, the derivatized aliquots may be recombined and reacted with one or more additional reagents in one reaction vessel. Alternatively, each aliquot may be subdivided into further aliquots and reacted as described herein.

Therefore, it will be obvious to the skilled artisan that the steps of dividing the portions, performing additional synthetic chemistry and recombining the portions, may each be carried out more than once. The steps of optionally dividing and recombining the resin-bound compound intermediates into portions are for purposes of varying the derivatization,

depending upon the type of diversity required for the library of end-product compounds being prepared. It will be recognized by the skilled artisan that the steps of dividing and recombining the resin-bound compound intermediates into a plurality of portions also has an impact on the size of the library being created. The methods described herein may be applied to the preparation of a large variety of compounds of formula (II).

According to this invention, after the additional synthetic chemistry has been performed on the resin-bound compound intermediates so that a library of molecularly diverse compounds of formula (II) has been prepared, the compounds can be separated and characterized by conventional analytical techniques known to the skilled artisan, for example infrared spectroscopy or mass spectroscopy. The compounds may be characterized while remaining resin-bound or they can be cleaved from the resin using the conditions described above, and then analyzed. In addition, a portion of resin-bound compound intermediates may be cleaved so that only a portion of the compound members are cleaved from the resin, characterized and analyzed, while leaving the remaining portion of the compound members of the library bound to the resin as derivatized resin-bound compound intermediates. It will be recognized that this library is considered to be a "partially cleaved" library of derivatized compounds, i.e., the library comprises (a) derivatized compounds which are cleaved from the resin and (b) derivatized compounds which remain resin-bound. Alternatively, if all of the resin-bound compound intermediates are cleaved so that all of the compound members of the library are cleaved from the resin, a "fully-cleaved" library of compounds is created.

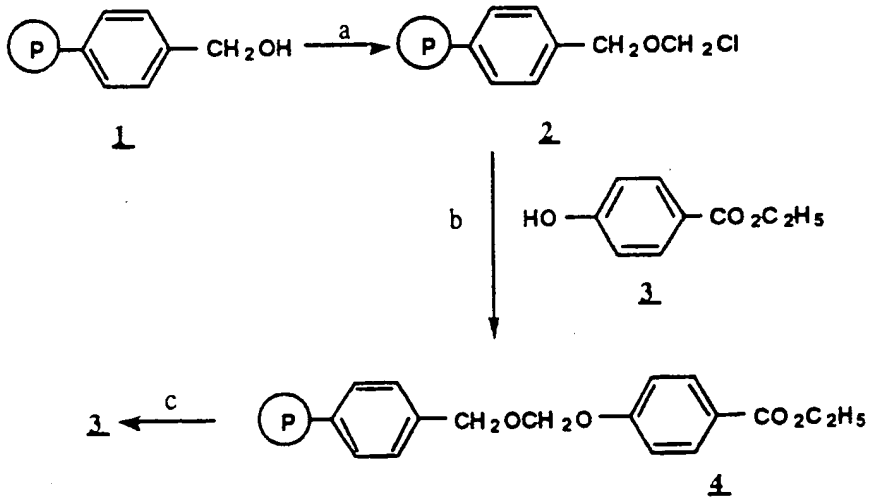
General Methods of Preparation

Given the following schemes which depict specific embodiments of the instant invention, one of ordinary skill in the art will be able to make and use the novel resins and linkers disclosed in order to prepare, by resin-bound synthesis, a variety of individual compounds, as well as libraries of molecularly diverse compounds, each of which will have a -COOH, cyclic or acyclic amide, cyclic or acyclic sulfonamide, hydroxy, -NH or -SH group attached to the compound at the position of cleavage from the resin. Generally, the resin of formula (I) is prepared, as described in detail below. A compound(s) comprising at least one heteroatom is coupled thereto using conditions well known in the art to produce a resin-bound compound intermediate. Additional synthetic chemistry known in the art is performed on the compound portion of the resin-bound compound intermediate so that a

resin-bound precursor to a compound(s) of formula (II) is produced. The final derivatized precursor to the compound(s) of formula (II) is either cleaved from the resin or allowed to remain resin-bound. The final compound of formula (II), whether resin-bound or cleaved from the resin is screened for pharmacological activity. Compounds which are active in the screen are characterized using conventional analytical and spectrographic techniques.

A chloromethoxymethylpolystyrene resin of the formula (I) wherein P is polystyrene; Z is phenyl; X is O; W is chlorine; and R^1, R^2, R^3 and R^4 are each hydrogen (see 2-Scheme 1) is prepared as shown in Scheme 1 by reaction of commercially available hydroxymethylpolystyrene resin (1-Scheme 1) with, e.g., trioxane and hydrochloric acid in a suitable nonprotonic solvent. Further reaction with the anion of a phenol, such as 3-Scheme 1, provides resin-bound compound intermediates such as 4-Scheme 1. These may be further derivatized by additional synthetic chemistry to form further compounds of interest which are also bound to the resin. The derivatized resin-bound compounds may be liberated from the resin to produce compounds of formula (II) by, e.g., treatment with an acid such as TFA.

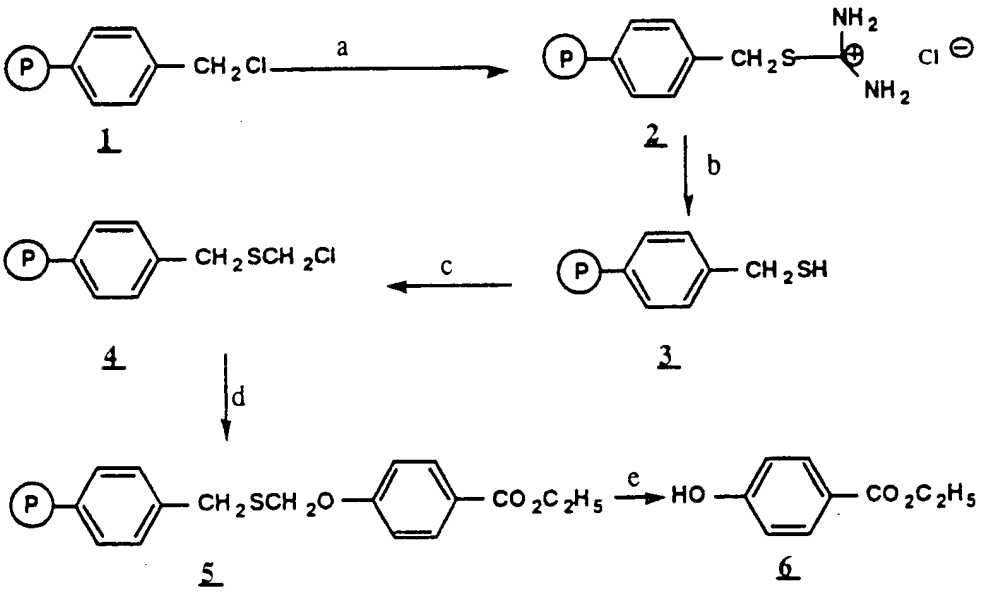
Scheme 1



(a) trioxane, HCl, dioxane; (b) NaH, THF; (c) 25% TFA, CH_2Cl_2

The preparation of a chloromethylthiomethylpolystyrene resin of the formula (I) wherein P is polystyrene; Z is phenyl; X is S; W is chlorine; and R^1, R^2, R^3 and R^4 are each hydrogen (see 4-Scheme 2) is shown in Scheme 2. Reaction of chloromethylpolystyrene (1-Scheme 2) with thiourea gives the thiouronium salt (2-Scheme 2) which, on basic hydrolysis gives mercaptomethylpolystyrene (3-Scheme 2). Reaction of 3-Scheme 2 with a source of formaldehyde and HCl gives chloromethylthiomethylpolystyrene (4-Scheme 2). Further reaction of 4-Scheme 2 with the anion of a phenol, such as 3-Scheme 1, provides resin-bound compound intermediates such as 5-Scheme 2. These may be further derivatized by additional synthetic chemistry to form compounds of interest which are also bound to the resin. The derivatized resin-bound compounds may be liberated from the resin to produce compounds of formula (II) by, e.g., treatment with an acid such as TFA.

Scheme 2

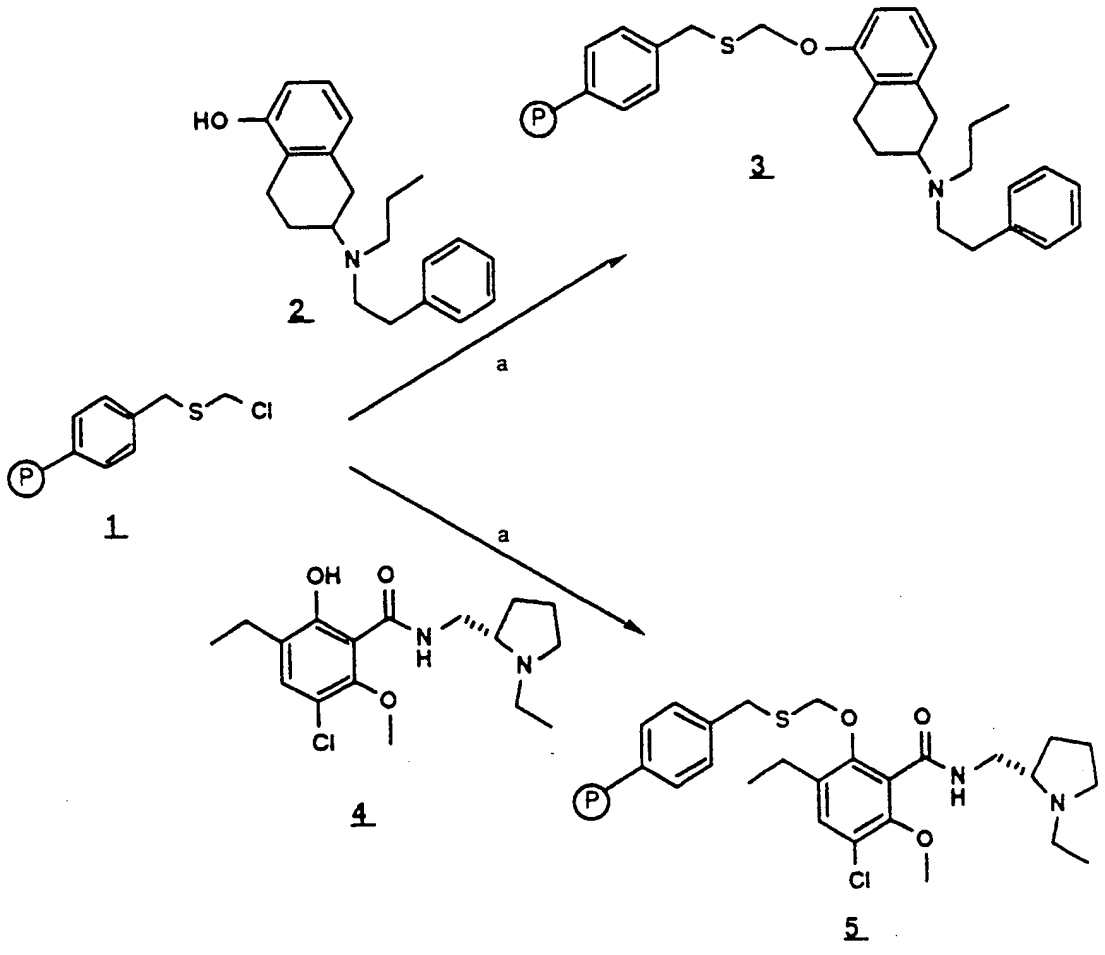


(a) Thiourea, DMF; (b) KOH, THF, H_2O; (c) s-trioxane, HCl, dioxane-ethyl ether; (d) ethyl 4-hydroxybenzoate, NaH, THF; (e) 25% TFA, CH_2Cl_2

Scheme 3 shows the attachment of several dopaminergics to a resin of formula (I), wherein P is polystyrene; Z is phenyl; X is S; W is chlorine; and R^1, R^2, R^3 and R^4 are each hydrogen (see 1-Scheme 3), via thioacetal linkages. After optional derivatization with

additional synthetic chemistry, these compounds are readily liberated from the resin by treatment with acid to give a compound of formula (II). For example, reaction of the phenol 2-Scheme 3 with a base, e.g., Cs_2CO_3, to form its anion followed by reaction with chloromethylthiomethylpolystyrene (1-Scheme 3) gave the resin bound compound 3-Scheme 3. A similar sequence using the dopamine antagonist eticlopride (4-Scheme 3) gave the resin bound antagonist 5-Scheme 3. Treatment of these thioacetal linked resin-bound compound intermediates with, e.g., 25% TFA in methylene chloride, produced the free compounds of formula (II).

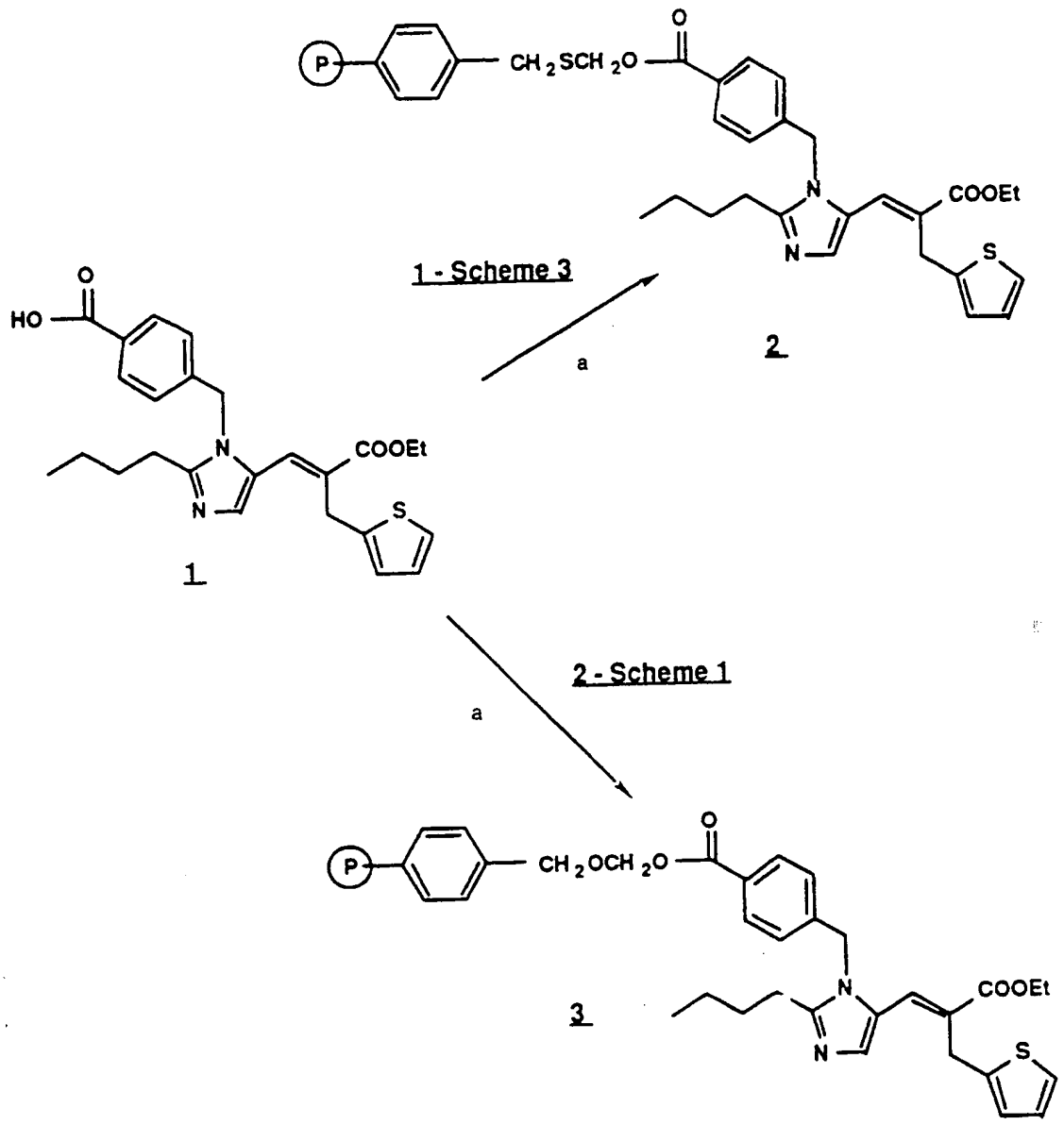
Scheme 3



(a) Cs_2CO_3, DMF

Scheme 4 shows the use of the acetal and thioacetal linkages to join acids to the resin by means of an ester bond. An anion of the acid 1-Scheme 4, created by conventional techniques, was reacted, in one case with the chloromethylthiomethyl resin 1-Scheme 3, and in the other case with the chloromethoxymethyl resin 2- Scheme 1, to give the compound intermediates, 2-Scheme 4 and 3-Scheme 4, respectively, each of which was bound to the resins by thioacetal or acetal linkages, respectively. These compound intermediates may be further derivatized by additional synthetic chemistry to form compounds of interest which are also bound to the resin. These derivatized compounds can be easily cleaved by acid, e.g., 25% TFA in methylene chloride.

Scheme 4



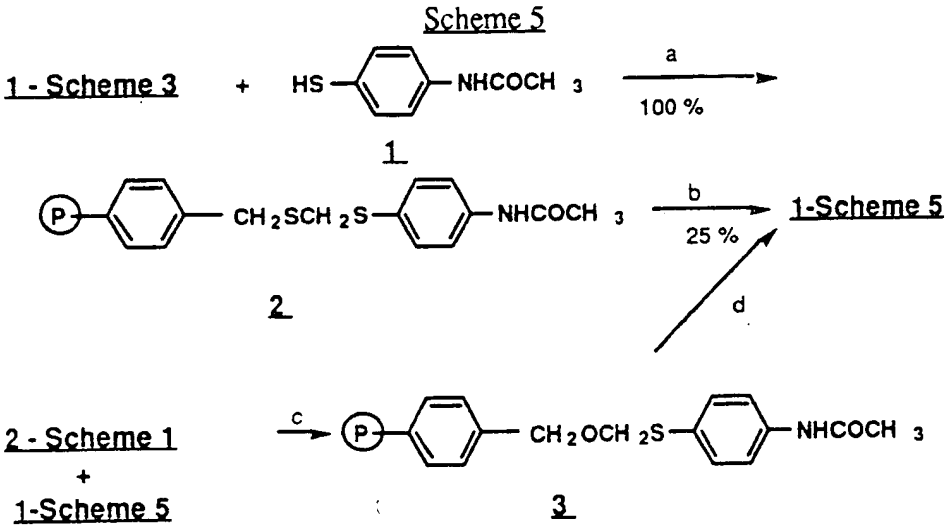
(a) Cs_2CO_3, DMF

Scheme 5 shows the attachment of a thiol to a resin via a dithioacetal and a thioacetal linkages. In particular, the cesium mercaptide was reacted with the resin 1-Scheme 3 to give 2-Scheme 5 wherein the compound, 1-Scheme 5, is bound to the resin (1-Scheme 3) by a dithioacetal linkage. Similarly, the mercaptide of 1-Scheme 5 was reacted with the chloromethoxymethyl resin, 2-Scheme 1, to give 3-Scheme 5 wherein the compound, 1-Scheme 5, is bound to the resin (2-Scheme 1) by a thioacetal linkage. The thioacetal linkage was readily cleaved by acid, but the dithioacetal linkage required

prolonged treatment with strong acid or metal ions such as silver or mercury for cleavage. This differentiation may be useful in that the compound of interest may be attached via the thioacetal linker while a tag for recording the chemical history of the bead could be attached via the dithioacetal linker. Thus the compound could be released first for biological assays, and the tags of the active beads could be read later to identify the active compound. See, for example, a description of synthesis using tags in WO 94/08051, published April 14, 1994, the relevant subject matter of which is incorporated herein by reference.

If the liberated compound of formula (II) is a thiol, desulfurization after release from the resin, for example with Raney nickel, gives the compound with a hydrogen at the position which was attached to the resin.

Scheme 5



(a) Cs_2CO_3, DMF, 24 hr; b) 20 % TFA, CH_2Cl_2, 1.5 hr.; c) 18 Crown 6, Cs_2CO_3, THF; (d) TFA reflux, 18 hr.

The residues attached to the resin through these ether and/or sulfide linkages may be reacted with many of the reagents normally used in synthetic organic chemistry to generate resin-bound combinatorial libraries for use in screening for activity as drugs. In addition non-resin-bound combinatorial libraries may be readily obtained by cleavage in acidic media. The dithioacetal linkers are resistant to cleavage under weakly acidic conditions. Therefore, the use of these linkers is especially suitable for carrying out

additional synthetic chemistry on a resin-bound compound intermediate, specifically when the additional chemistry requires acidic reagents.

As will be obvious to the skilled artisan, if the chloromethylthiomethylpolystyrene resin (4-Scheme 2) is coupled to a thiol compound, after derivitization of the resin-bound compound, the liberated compound of formula (II) wherein A_3 is $-SR^8$, is a thiol, which on desulfurization, for example with Raney nickel, gives a compound with a hydrogen at the position which was attached to the resin.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following examples further illustrate the synthesis and use of the compounds of this invention. The following examples are, therefore, to be construed as merely illustrative and not a limitation of the scope of the present invention in any way.

EXAMPLES:

Example 1: Preparation of chloromethoxymethylpolystyrene resin (2-Scheme 1)

A gently stirred mixture of hydroxymethylpolystyrene (1% divinylbenzene crosslinked, 0.8 mM OH/g) (1.86g, 1.488 mM) and s-trioxane (0.54 g, 5.952 mM) in 2:1 anhydrous 1,4-dioxane/ether (60 mL) was saturated with anhydrous hydrogen chloride while keeping the reaction mixture below 10°C. The mixture was stirred in the cold for an additional 3 hr, the product collected on a coarse glass-fritted filter, washed successively with 1,4-dioxane (3x50 mL), methylene chloride (5x50 mL), and ether (5x50 mL), dried at 0.1 mm Hg at ambient temperature to provide the title compound (1.93 g, 100%). Fourier Transform Infrared Spectroscopy ("Ft IR") (KBr) 637.601 cm^{-1} (Cl). Anal. calcd: Cl, 2.73; found: Cl, 2.39.

Example 2: Preparation of ethyl 4-phenoxymethoxymethylpolystyrenebenzoate resin-bound intermediate (4-Scheme 1)

Dry 97% sodium hydride (0.60 g, 2.425 mM) was added in one portion to a stirred solution of ethyl p-hydroxybenzoate (0.3361 g, 2.022 mM) in anhydrous THF (20 mL). The mixture was stirred until evolution of hydrogen ceased (0.5 hr) then chloromethoxymethylpolystyrene (0.674 mM Cl/g) (1.00 g, 0.674 mM) was added and heated at 70°C for 24 hr. The product was collected on a coarse glass-fritted filter, washed successively with

THF (3x30 mL), 1:1 THF:H_2O (3x30 mL), THF (3x20 mL), and methanol (4x30 mL) to provide 1.01g (93%) of title compound. IR (KBr) 1700 cm^{-1} (C=O).

A sample of the product (0.50 g) was stirred in 25% TFA/methylene chloride (4 mL) for 5 min. at ambient temperature. Thin-Layer Chromatography ("TLC") (silica gel, 10% methanol/chloroform) analysis indicated that the ethyl p-hydroxybenzoate was cleaved off the resin. Evaporation of the filtrate provided 0.040 g (71%) of the ester and a small amount the corresponding benzoic acid.

Example 3: Preparation of ester of (E)-α-[[2-butyl-1-[4-carboxyphenyl)methyl]-1-*H*-imidazol-5-yl]methylene-2-thiophenepropanoic acid ethyl ester and hydroxymethyloxy-methyl-polystyrene resin

The pH of a solution of (E)-α-[[2-butyl-1-[4-carboxyphenyl)methyl]-1-*H*-imidazol-5-yl]methylene-2-thiophenepropanoic acid ethyl ester (see U.S. Patent 5,185,351, issued February 9, 1993, Example 41, incorporated herein by reference, 1.00 g, 2.21 mM) in 15 ml of EtOH and 3 ml of water was brought to 7.03 by addition of aqueous 20% Cs_2CO_3. The solvents were evaporated under vacuum, and the residue dried by successive additions of EtOH and toluene followed by evaporation under vacuum. The residue was dried at 90°C at 0.1 mm Hg to provide 1.31 g of the Cs salt of the benzoic acid moiety. This was dissolved in 35 ml of THF and 1.32 g (0.737 mmol) of chloromethoxymethylpolystyrene (2-Scheme 1) added. The suspension was stirred gently at 45°C for 36 hr, and then at ambient temperature for an additional 36 hr. The mixture was filtered and the solid resin washed first with THF, and then progressively with THF to neat H_2O, H_2O to neat THF, THF to neat CH_2Cl_2, and finally CH_2Cl_2 to neat Et_2O. Drying at 80°C at 0.1 mm of Hg gave 1.52 g of resin, IR (KBr) 1715 cm^{-1}, 1695 cm^{-1} indicative of 2 carbonyl groups. Anal. calcd: N, 1.27; found: N, 1.06 for 0.378 mmol of ligand per dry gram of resin.

A sample of this resin in a small vial in a closed jar was exposed to vapor from a small beaker of a 3% solution of ethanedithiol in methylene chloride for 1.5 hr. Then a small beaker of TFA was placed in the jar and allowed to stand for 18 hr. A methylene chloride extract of a few beads showed the presence of the starting acid both by TLC and Mass Spectroscopy ("MS").

Example 4: Preparation of the chloromethylthiomethylpolystyrene resin (4-Scheme 2)

(a) Thiouroniummethylpolystyrene hydrochloride (2-Scheme 2)

A mixture of Merrifield's peptide resin (available from Aldrich; 2% crosslinked, 1.015 mM Cl/g) (5.00 g, 5.075 mM) and thiourea (1.55 g, 20.362 mM) in DMF (50 mL) were gently stirred at ambient temperature for 48 hr. The product was collected on a coarse glass-fritted filter, washed successively with DMF (3x100 mL), THF (3x100) mL), methylene chloride (3x100 mL), and methanol (3x100 mL). The material was air dried to provide 5.38 g (100%) of product. IR (KBr) 3410-2800 cm^{-1} (b), 1630 cm^{-1} (s). Anal. calcd: N, 2.64; found: N, 2.52.

(b) Mercaptomethylpolystyrene resin (3-Scheme 2)

The thiouronium salt (2-Scheme 2) (4.75 g, 4.821 mM) was suspended in 3:2 THF:H_2O (50 mL), potassium hydroxide (0.94 g, 16.753 mm) added, and the suspension gently stirred and heated at reflux for 18 hr. The product was isolated on a coarse glass-fritted filter, washed successively with 1:1 THF:H_2O (3x50 mL), H_2O (2x50 mL), 75:25 THF:H_2O (3x50 mL), 9:1 THF:H_2O (3x50 mL), THF (3x50 mL), methylene chloride (3x50 mL), and methanol (4x50 mL). The material was air dried to provide 4.53 g (95%) of product. IR (KBr) 2530 cm^{-1} (SH). Anal. calcd: S, 3.26; found: S, 3.11.

(c) Chloromethylthiomethylpolystyrene resin (4-Scheme 2)

A stirred mixture of mercaptomethylpolystyrene resin (3-Scheme 2) (4.25 g, 4.1221 mM) and s-trioxane (1.55 g, 17.207 mM) in 2:1 anhydrous 1,4-dioxane/ether (150 mL) was placed in an ice-bath at -10°C and saturated with anhydrous hydrogen chloride (1.25 hr). The mixture was then stirred at ambient temperature for 18 hr. The product was collected on a coarse glass-fritted filter, washed successively with 1,4-dioxane (3x30 mL), THF (4x50 mL), methylene chloride (4x50 mL), and ether (4x50 mL), dried at 40°C, 0.1 mm Hg. The yield was 4.41 g (99%). IR (KBr) 640 cm^{-1} (Cl). Anal. calcd: Cl, 3.28; S, 2.97; found: Cl, 2.86; S, 2.91.

Example 5: Preparation of ethyl 4-phenoxythiomethylmethylpolystyrenebenzoate resin (5-Scheme 2)

A mixture of ethyl 4-hydroxybenzoate (0.0532 g, 0.3024 mM) and cesium carbonate (0.1310 g, 0.4022 nM) in DMF (5 mL) was stirred at ambient temperature for 4 hr. Chloromethylthiomethylpolystyrene resin (4-Scheme 2) (0.8066 mM Cl/g) (0.1250 g, 0.1008 mM) was added in one portion and stirred at ambient temperature for 18 hr. The

resin-intermediate was collected on a coarse fritted glass filter, washed successively with 3x30 mL portions of DMF, 1:1 DMF/H_2O, water, DMF, THF, methylene chloride, and methanol, and then air-dried to provide 0.1000 g (72%) of product. IR (KBr) 1700 cm^{-1} (C=O).

A small sample of 5-Scheme 2 was treated with 25% TFA/methylene chloride at ambient temperature for 5 min. TLC (silica gel, 10% methanol/chloroform) analysis indicated that the ethyl 4-hydroxybenzoate was cleaved off the resin.

Example 6: Preparation of 6-(methoxythiomethylpolystyrene)-S(-)-eticlopride resin

A mixture of S(-)-eticlopride hydrochloride (S(-)-3-chloro-5-ethyl-N-[(1-ethyl-2-pyrrolidinyl)methyl]-6-hydroxy-2-methoxybenzamide hydrochloride) (0.2500 g, 0.6626 mM) and cesium carbonate (0.64477 g, 1.9880 mM) in DMF (10 mL) was stirred at ambient temperature for 3 hr. Chloromethylthiomethylpolystyrene resin (0.8066 mM Cl/g) (0.2770 g, 0.2234 mM) was added in one portion, stirred at ambient temperature for 18 hr. The resin-intermediate was isolated as in Example 3. The product was dried at 40°C, 0.1 mm Hg. The yield was 0.3024 g (88%). IR (KBr) 3340 cm^{-1} (NH), 1651 cm^{-1} (C=O). Anal. calcd: N, 1.80; found: N, 1.13.

Example 7: Preparation of ester of (E)-α-[[2-butyl-1-[4-carboxyphenyl)methyl]-1-*H*-imidazol-5-yl]methylene-2-thiophenepropanoic acid ethyl ester and hydroxymethylthiomethyl-polystyrene resin

The procedure of Example 3 was used except that the esterification was carried out using DMF as the solvent and the reaction was heated at 45°C for 48 hr. The resin product was obtained in 96% yield. IR (KBr) 1710 cm^{-1} and 1690 cm^{-1} indicating 2 carbonyls. Anal. calcd: N, 1.69; found: N, 1.52 indicating 0.543 mmol ligand per dry gram of resin. This resin also cleaved to liberate the starting acid when exposed to vapors of methylene chloride, ethanedithiol, and TFA.

Example 8: Preparation of 4-acetamidophenylthiomethylthiomethylpolystyrene resin (2-Scheme 5)

A mixture of 4-acetamidothiophenol (available from Aldrich, 80.9 mg, 0.48 mmol) and 173.5 mg (O.532 mmol) of Cs_2CO_3 in 10 ml of DMF was stirred at ambient temperature for 24 hr. Then 150 mg (0.121 meq) of chloromethylthiomethylpolystyrene

resin (1-Scheme 3) was added and the stirring continued for 24 hr at ambient temperature. The resulting resin intermediate (2-Scheme 5) was collected on a coarse fritted glass filter and washed in turn with DMF, 1:1 DMF - H_2O, H_2O, DMF, THF, methylene chloride, and methanol. Drying under 0.1 mm Hg vacuum at 40°C gave 167.2 mg of product. IR (KBr) 3300 cm^{-1}, 3290 cm^{-1} (NH), 1680 cm^{-1} (CO).

A suspension of a small sample of the product was refluxed in a solution of 1% veratrol in TFA for 1.5 hr. TLC of the solution showed the presence of 4-acetamidothiophenol (1-Scheme 5). IR suggested that about 25% of the ligand had been cleaved from the resin.

Example 9: Preparation of 4-acetamidophenylthiomethylmethoxymethylpolystyrene resin

The reaction of 4-acetamidothiophenol and chloromethoxymethylpolystyrene resin was carried out as in Example 8, except that 18-crown-6 was added as a catalyst in the alkylation step. The product was isolated in 96% yield. IR (KBr) 1690 cm^{-1} (C=O).

Example 10: Preparation of 2-(phenylethyl-N-propyl)amino-5-polystyrenemethyl-thiomethoxytetralin resin

The reaction of 2-(phenylethyl-N-propyl)amino-5-hydroxytetralin and chloromethylthiomethylpolystyrene resin (4-Scheme 2) was carried out as in Example 5 to give the product as a light tan resin (78% yield). Anal. calcd: N, 0.93; found: N, 0.71 equivalent to 0.507 mmol ligand per gram of dry resin.

A small sample of resin product was treated with 25% TFA in methylene chloride at room temperature for 5 min. TLC of the solution showed the presence of the starting phenol in reasonable quantity.

It will be clear to the skilled artisan that the linkers and polymer resins of this invention may be used in a variety of combinatorial methods for synthesizing and identifying a large number of molecularly diverse compounds, simultaneously. For example, the instant invention may be applied to (i) the "multi-pin" method described in Geysen et al., *Proc. Natl. Acad. Sci. USA.*, **81**, p. 3998 (1984); U.S. Patent 4,708,871 (1987); Geysen et al., *Bioorg. Med. Chem. Lett.*, **3**, p.397 (1993); and European Patent 138,855 (1991); (ii) the "tea-bag" approach described in Houghten, R.A., *Proc. Natl. Acad. Sci. USA.*, **82**, p. 5131 (1985); and Houghten et al., *Nature*, **354**, p. 84 (1991); (iii)

chemical synthesis on a "chip" described in Fodor et al., *Science*, **251**, p. 767 (1991) and U.S. Patent 5,143,854 (1992); and (iv) synthesis using tags described in WO 94/08051, published April 14, 1994.

In addition, the compounds may be screened in assays which have been developed for determining lead compounds as pharmaceutical agents. For reasons of efficiency, the components of the library are screened in groups of multiple compounds. Therefore, once the library of compounds has been synthesized, there must be some method to deconvolute the results of screening such that individual active compounds can be identified. Based upon the disclosure herein, it will be clear to the skilled artisan that there are many methods for deconvolution of the combinatorial library. For example, if the compounds of the library are screened on a solid support, they may be physically segregated so that individual active compounds may be directly selected and identified. In contrast, if the compounds of the library are cleaved from the resin and tested as soluble mixtures, the library may be deconvoluted in an iterative approach, which involves resynthesis of mixtures of decreasing complexity until a single compound is identified, or in a scanning approach, in which the various substituents on the compound, are evaluated independently and the structure of active compounds are determined deductively. For an explanation of the iterative and scanning approaches to deconvolution of a combinatorial library of compounds, see, for example, Houghten et al., *Nature*, **354**, p. 84 (1991) and Still et al., WO 94/08051, published April 14, 1994.

Biological Assays:

(I) A representative binding assay is as follows. Other binding assays or functional assays that are known by, or that would be obvious to the skilled artisan, may be performed as well. Tissue containing the appropriate target receptor are homogenized, filtered through cheesecloth and centrifuged at 1500 x g for 10 minutes. The supernatant is decanted and the pellet is resuspended in an appropriate incubation buffer, e.g. 75 mM Tris·HCl, pH 7.4 containing 12.5 mM $MgCl_2$ and 1.5 mM EDTA. Membranes equivalent to 100 g protein are incubated with 50 pmol radiolabeled receptor ligand and an appropriate amount of the test library mixture in a total volume of 500 l for 1 hr. at 37°C. The binding reaction is terminated by dilution with the addition of 5 ml of cold incubation buffer and the bound tracer is separated from free by filtration on Whatman GF/C filter

paper. The filter paper is washed several times with cold incubation buffer and then counted to determine the amount of bound ligand.

Specific binding is defined as the portion of radiolabeled receptor ligand binding which can be competed with by a high concentration of unlabeled receptor ligand. The presence of a competing ligand in the library test mixture is evidenced by a reduction in specific binding of the radiolabeled receptor ligand in the presence of the library test mixture.

(II) An additional assay that is effective and extremely useful for testing the compounds prepared according to this invention is disclosed by Lerner et al., *Proc. Natl. Acad. Sci. U.S.A.*, **91**(5), pp. 1614-1618 (1994), which is incorporated by reference herein.

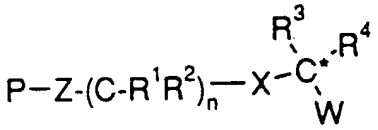
It will be recognized by one of ordinary skill in the art that compounds of formula (II), made by the instant methods, may be tested in conventional assays which are suitable for screening for enzyme inhibitors, channel blockers and receptor ligands, for example, G-protein coupled receptor ligands.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore any examples are to be construed as merely illustrative and not a limitation on the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed, are defined as follows.

What is claimed is:

1. A method for preparing a resin-bound compound, said method comprising the steps of:

(i) attaching a compound comprising at least one heteroatom to a polymeric resin of formula (I):



Formula (I)

wherein X is O, S, or N-R, wherein R is hydrogen, alkyl, aryl or arylalkyl; P is a polymer support; Z is a bond, optionally substituted aryl or optionally substituted heteroaryl, wherein the optional substituents are alkyl, aryl, nitro, halogen or methoxy, or Z is -COOR', wherein R' is (C_2 to C_{20}) alkyl optionally having one or more intervening aryl groups; W is a leaving group that is readily displaceable by an oxygen, nitrogen or sulfur anion; R^1, R^2, R^3 and R^4 are, independently from one another, hydrogen, (C_1 to C_4) alkyl, (C_2 to C_{10}) cyclic alkyl or optionally substituted aryl; and n is an integer from 0 to 10;

whereby the attachment occurs by displacing the leaving group W to form a resin-bound compound intermediate having a carbon atom-heteroatom bond at the carbon indicated with an asterisk; and

(ii) performing additional synthetic chemistry on the the resin-bound compound intermediate.

2. The method of claim 1, further comprising the step of cleaving the resin-bound compound intermediate so that the compound thus formed has a -COOH, cyclic or acyclic amide, cyclic or acyclic sulfonamide, hydroxy, -NH or -SH group at the position where it was bound to the resin.

3. A method for preparing a library of molecularly diverse compounds each comprising at least one heteroatom, said method comprising the steps of:

(i) attaching a heteroatom of each of a plurality of compounds to an individual polymeric resin of formula (I) by displacing each of the leaving groups W on the individual polymeric resins to give a plurality of resin-bound compound intermediates;

(ii) optionally dividing said resin-bound compound intermediates into a plurality of portions;

(iii) performing additional synthetic chemistry on the plurality of resin-bound compound intermediates to derivatize said compounds; and

(iv) optionally recombining the portions.

4. The method of any of claims 1, 2 or 3 wherein the compound being prepared comprises a structure of formula (II):

A-H

Formula (II)

wherein A is A_1, A_2, A_3, A_4, A_5, A_6, A_7, or A_8;

A_1 is $-OR^5$, wherein R^5 is optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbonyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted heteroarylalkyl, optionally substituted heterocyclic, optionally substituted heteroalkyl, optionally substituted heterocyclicalkyl, or optionally substituted alkylheteroalkyl;

A_2 is $-NR^6R^7$, wherein R^6 and R^7 are the same or different and are hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted heteroarylalkyl, optionally substituted heterocyclic, optionally substituted heteroalkyl, optionally substituted heterocyclicalkyl, or optionally substituted alkylheteroalkyl, provided that R^6 and R^7 cannot both be hydrogen; or wherein R^6 and R^7, together with the nitrogen to which they are bound, form an optionally substituted, saturated or unsaturated, 4-, 5-, 6- or 7-membered ring;

A_3 is $-SR^8$, wherein R^8 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted cycloalkyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted

heteroarylalkyl, optionally substituted heterocyclic, optionally substituted heteroalkyl, optionally substituted heterocyclicalkyl, or optionally substituted alkylheteroalkyl;

A_4 is R^9-COO^-, wherein R^9 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted cycloalkyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted heteroarylalkyl, optionally substituted heterocyclic, optionally substituted heteroalkyl, optionally substituted heterocyclicalkyl, or optionally substituted alkylheteroalkyl;

A_5 is -NR^{10}-$C(O)R^{11}$, wherein R^{10} and R^{11} are the same or different and are optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted heteroarylalkyl, optionally substituted heterocyclic, optionally substituted heteroalkyl, optionally substituted heterocyclicalkyl, or optionally substituted alkylheteroalkyl; or wherein R^{10} and R^{11}, together with the nitrogen and carbonyl to which they are bound, form an optionally substituted, saturated or unsaturated, 4-, 5-, 6- or 7-membered ring;

A_6 is -NR^{12}-SO_2R^{13}, wherein R^{12} and R^{13} are the same or different and are optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted heteroarylalkyl, optionally substituted heterocyclic, optionally substituted heteroalkyl, optionally substituted heterocyclicalkyl, or optionally substituted alkylheteroalkyl; or wherein R^{12} and R^{13}, together with the nitrogen and sulfone to which they are bound, form an optionally substituted, saturated or unsaturated, 4-, 5-, 6- or 7-membered ring;

A_7 is -O-$(CH_2)_m$-$C(O)R^{14}$, wherein m is an integer from 0 to 10; and R^{14} is hydrogen, hydroxyl, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted heteroarylalkyl, optionally substituted heterocyclic, optionally substituted heteroalkyl, optionally substituted heterocyclicalkyl, or optionally substituted alkylheteroalkyl; or wherein when m is an integer from 1 to 10, R^{14} may form an optionally substituted, saturated or unsaturated, 4-, 5-, 6- or 7-membered ring together with one of the methylene carbons; and

A_8 is -O-$(CH_2)_r$-A'-C(O)R^{15}, wherein r is an integer from 0 to 10; A' is O, N, or S; and R^{15} is hydrogen, hydroxyl, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted heteroarylalkyl, optionally substituted heterocyclic, optionally substituted heteroalkyl, optionally substituted heterocyclicalkyl, or optionally substituted alkylheteroalkyl; or R^{15} may form an optionally substituted, saturated or unsaturated, 4-, 5-, 6- or 7-membered ring together with one of the methylene carbons; provided that when A' is O or S, r must be an integer from 1 to 10.

5. The method of any of claims 1, 2 or 3 wherein W is chlorine, bromine, iodine, -OSO_2R", wherein R" is alkyl, optionally substituted aryl, or perfluoroalkyl.

6. The method of claim 3 wherein the steps of (ii) dividing the portions, (iii) performing additional synthetic chemistry, and (iv) recombining the portions, are carried out more than once.

7. The method of claim 3 wherein the derivatized compounds are partially cleaved from the resin.

8. The method of claim 7 wherein the compounds which are cleaved from the resin are compounds of formula (II), wherein A_3 is -SR^8, and further wherein said compounds are treated with Raney nickel to convert the HSR^8 moiety into an HR^8 moiety.

9. The method of claim 3 wherein the derivatized compounds are fully cleaved from the resin.

10. The method of claim 9 wherein the compounds are compounds of formula (II), wherein A_3 is -SR^8, and further wherein said compounds are treated with Raney nickel to convert the HSR^8 moiety into an HR^8 moiety.

11. The method of any of claims 1, 2 or 3 wherein the compound is attached to the resin by a linker group comprising -Z-$(CR^1R^2)_n$-X-C*-R^3R^4-, wherein Z is an

optionally substituted aryl group or an optionally substituted heteroaryl group, or Z is -COOR', wherein R' is (C_1 to C_4) alkyl; X is a heteroatom; R^1, R^2, R^3 and R^4 are, independently from one another, hydrogen, (C_1 to C_4) alkyl, (C_2 to C_{10}) cyclic alkyl or optionally substituted aryl; and n is an integer from 0 to 10.

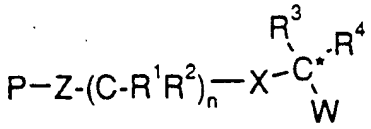
12. The method of claim 11 wherein the optional substituents of the moiety Z are nitro, halogen or methoxy.

13. The method of claim 11 wherein the linker group is -Ph-CH_2-S-CH_2- or -Ph-CH_2-O-CH_2-.

14. The method any of claims 1, 2 or 3 wherein P is a cross-linked polystyrene resin, a polyethylene glycol-polystyrene based resin, or a polypropylene glycol based resin.

15. The method of any of claims 7 or 9 wherein the compounds are cleaved from the resin by HF, TFA, HCl, HBr, H_2SO_4, pyridinium hydrofluoride, triflic acid, BF_3, methanesulfonic acid or mixtures thereof.

16. A compound of formula (I)



Formula (I)

wherein X is O, S, or N-R, wherein R is hydrogen, alkyl, aryl or arylalkyl; P is a polymer support; Z is a bond, optionally substituted aryl or optionally substituted heteroaryl, wherein the optional substituents are alkyl, aryl, nitro, halogen or methoxy, or Z is -COOR', wherein R' is (C_2 to C_{20}) alkyl optionally having one or more intervening aryl groups; W is a leaving group that is readily displaceable by an oxygen, nitrogen or sulfur anion; C* is a carbon which forms a carbon atom-heteroatom bond upon displacement of leaving group W; R^1, R^2, R^3 and R^4 are, independently from one another, hydrogen, (C_1 to C_4) alkyl, (C_2 to C_{10}) cyclic alkyl or optionally substituted aryl; and n is an integer from 0 to 10.

17. The compound of claim 16, wherein W is chlorine, bromine, iodine, $-OSO_2R'$, wherein R' is alkyl, optionally substituted aryl, or perfluoroalkyl.

18. A method for screening the compound prepared according to any of claims 1, 2 or 3 for receptor binding, comprising testing the compound in a suitable assay developed for determining activity as a receptor ligand.

19. The method of claim 18 wherein the the receptor is a G-protein coupled receptor.

20. The method of claim 18 wherein the compound that is screened comprises a compound attached to a polymeric resin by one carbon-heteroatom bond.

21. A method for screening the compound prepared according to any of claims 1, 2 or 3 as an enzyme inhibitor, comprising testing the compound in a suitable assay developed for determining activity as an enzyme inhibitor.

22. A method for screening the compound prepared according to any of claims 1, 2 or 3 as a channel blocker, comprising testing the compound in a suitable assay developed for determining activity as a channel blocker.

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :G01N 33/53; G01N 33/545; C07K 17/08

US CL :436/518, 501; 435/7.1; 530/334; 525/54.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 436/518, 501; 435/7.1; 530/334; 525/54.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, STN

search terms: structure search, solid-phase synthesis, resin

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US, A, 4,659,774 (WEBB ET AL.) 21 APRIL 1987, COLUMN 2, LINES 9-50.	1,4,14,16, 18 --- 2,3,5-13, 17, 19-22
Y	WO, A, 92/00091 (BIOLIGAND INC.) 09 JANUARY 1992, SEE PAGES 6, 9 AND 26-28.	2, 3, 5-13, 17,19-22
Y	US, A, 4,037,037 (PATCHORNIK ET AL.) 19 JULY 1977, COLUMNS 2-3.	2, 3, 5-13, 17,19-22
Y	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, VOLUME 90, ISSUED AUGUST 1993, DEWITT ET AL. "'DIVERSOMERS': AN APPROACH TO NONPEPTIDE, NONOLIGOMERIC CHEMICAL DIVERSITY", PAGES 6909-6913, SEE PAGE 6909.	2, 3, 5-13, 17,19-22

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
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"P"	document published prior to the international filing date but later than the priority date claimed		

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	INTERNATIONAL JOURNAL OF PEPTIDE AND PROTEIN RESEARCH, VOLUME 35, ISSUED 1990, FIELDS ET AL., "SOLID PHASE PEPTIDE SYNTHESIS UTILIZING 9-FLUORENYLMETHOXYCARBONYL AMINO ACIDS", PAGES 161-214, SEE TABLE I.	2,3,5-13, 17,19-22